APPENDIX 2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

◄ Previous Volume 325:533-538 August 22, 1991 Number 8 Next ►

Activation by extracellular nucleotides of chloride secretion in the airway epithelia of patients with cystic fibrosis

MR Knowles, LL Clarke, and RC Boucher

Abstract

BACKGROUND. Cystic fibrosis is characterized by abnormal electrolyte transport across the epithelia of the airways. In particular, there is excessive sodium absorption and deficient chloride secretion. Drugs that block excessive sodium absorption may provide clinical benefit in cystic fibrosis, but there are no available therapeutic agents to improve chloride secretion. In vitro studies in cultured human-airway epithelia indicate that triphosphate nucleotides (ATP and UTP) induce chloride secretion through apical-membrane purinergic receptors. METHODS. We tested the ability of nucleotides to induce chloride secretion in vivo in 9 normal subjects and 12 patients with cystic fibrosis by measuring responses of nasal transepithelial potential difference (PD) to superfusion of nucleotides. Changes in transepithelial bioelectric properties and the permeability of the apical membrane to chloride in response to extracellular (apical) UTP were determined with ion-selective microelectrodes in cultured nasal epithelia. RESULTS. ATP and UTP induced chloride secretion in vivo in both groups. At their maximal effective concentrations of 10(-4) M, ATP and UTP were more effective chloride secretagogues in the patients with cystic fibrosis (mean [+/- SE] change in PD, -19.8 +/- 1.4 mV and -15.0 +/- 1.7 mV, respectively) than in the normal subjects (-6.9 +/- 0.6 mV and -8.1 +/- 0.9 mV, respectively). Microelectrode studies established that extracellular UTP stimulated a larger increase in PD and chloride secretory current in epithelial cells from patients with cystic fibrosis than in cells from normal subjects, by actions localized to the apical membrane. CONCLUSIONS. Extracellular nucleotides are effective in vivo chloride secretagogues in the nasal epithelia of patients with cystic fibrosis. The equipotency of ATP and UTP suggests that the effect is mediated by P2 nucleotide receptors. Selected nucleotides, such as UTP or nucleotide analogues, should be investigated as therapeutic agents for lung disease in cystic

fibrosis.

Source Information

Department of Medicine, University of North Carolina, Chapel Hill 27599.

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